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14. ABSTRACT

Obstructive sleep apnea (OSA) consists of repetitive choking spells due to sleep-induced reduction of upper airway muscle tone. Millions of adults and children live unaware of this condition, which can have a profound affect on their health and quality of life. Obesity, gender, genetic, and hormonal factors mediate risk for OSA and interact in a multifaceted manner in the pathogenesis of this disease. Obesity is the most established and primary risk factor given that body mass index, visceral fat, and neck circumference are major predictors in the clinical expression of OSA. Many studies have shown weight loss or gain significantly impacts OSA severity. More recently, accumulating evidence indicates OSA promotes weight gain, obesity, and type II diabetes in a variety of ways, such that obesity and OSA form multiple interleaved vicious cycles. Thus, creative strategies to increase physical activity, improve diet, and otherwise facilitate weight management become particularly vital given the epidemics of obesity and OSA in the United States. In this regard, the American College of Sports Medicine recently launched the "Exercise is Medicine" (initiative exerciseismedicine.org). In the future, medications may emerge to treat obesity, OSA, and their sequelae with minimal side effects

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Obesity and obstructive sleep apnea: Or is it OSA and obesity?

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Abstract

Obstructive sleep apnea (OSA) consists of repetitive choking spells due to sleep-induced reduction of upper airway muscle tone. Millions of adults and children live unaware of this condition, which can have a profound affect on their health and quality of life. Obesity, gender, genetic, and hormonal factors mediate risk for OSA and interact in a multifaceted manner in the pathogenesis of this disease. Obesity is the most established and primary risk factor given that body mass index, visceral fat, and neck circumference are major predictors in the clinical expression of OSA. Many studies have shown weight loss or gain significantly impacts OSA severity. More recently, accumulating evidence indicates OSA promotes weight gain, obesity, and type II diabetes in a variety of ways, such that obesity and OSA form multiple interleaved vicious cycles. Thus, creative strategies to increase physical activity, improve diet, and otherwise facilitate weight management become particularly vital given the epidemics of obesity and OSA in the United States. In this regard, the American College of Sports Medicine recently launched the "Exercise is Medicine" (initiative exerciseismedicine.org). In the future, medications may emerge to treat obesity, OSA, and their sequelae with minimal side effects. However, there are effective ways to approach these problems now without waiting for "the magic pill".
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Keywords: Physical inactivity; Exercise; Sleep disorder; Obese; Ethnicity; Body weight

1. Introduction

Obstructive sleep apnea (OSA) is a disorder characterized by partial or complete narrowing of the pharyngeal airway during sleep, resulting in repeated episodes of airflow cessation, oxygen desaturation, and sleep interruption. Over the past 25 years, the prevalence of overweight and obesity in developed countries has increased significantly across all age groups and ethnic populations, and consequently has contributed to the public health burden of sleep apnea [1]. In spite of the high and increasing prevalence of OSA, most primary care physicians in the United States under-recognize the public health impact of this disease [2]. In fact, it has been estimated that 60–80% of adults Americans with OSA are not diagnosed [3–5] and this proportional may be even greater in children [6,7]. In recent years, the prevalence of OSA has increased especially rapidly in obese children.

Based on the World Health Organization and The National Institutes of Health criteria for defining overweight and obesity [8], their prevalence now constitutes an epidemic [1,2,9]. In the United States, ∼55% of men and 50% of women are presently overweight or obese [2,9]. The connection between OSA and obesity is very complex and likely represents an interaction of biological (i.e., sex, racial, genetic, and neurohormonal) and lifestyle factors. Therefore, understanding the mechanisms of obesity-related OSA is important for prevention and medical treatment, especially in children.

The purpose of this review is to explore the relationship of obesity and sleep apnea from epidemiological studies, describe the complex, interleaved vicious cycles that connect the two diseases, and raise some intriguing questions concerning treatment of obesity and sleep apnea in children and adults.

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2. Obesity and ancillary risk factors for OSA

Numerous risk factors including overweight/obesity, age, sex, race/ethnicity, and heritable factors are well documented in the pathogenesis of sleep apnea. Nevertheless, obesity has been consistently demonstrated as one of the greatest sleep apnea risk factors [10]. Several cross-sectional studies have consistently found a relationship between body mass index (BMI) and the risk of OSA. The reported prevalence of sleep apnea ranges from 40 to 90% in individuals with a body mass index >40 kg/m^2 (severe obesity) [8,11]. Significant sleep apnea is present in 40% of obese persons and over 70% of sleep apnea patients present with obesity [12].

Obesity is the only major OSA risk factor that is reversible. Weight reduction in the short term (1–2 years) leads to a better metabolic regulation of patients with OSA [5]. A prospective study in Wisconsin residents showed that a 10% weight loss predicted a 26% decrease in sleep apnea severity (i.e., apnea hypoapnea index (AHI)) (Fig. 1) [11]. Furthermore, reduced apnea frequency followed weight loss in another cohort study [13]. Although, the exact mechanisms of weight loss and decreased OSA symptoms are not fully understood, factors such as reduced fat deposition [14] in and near airway structures and improved neurophysiologic regulation of respiration are likely important [15]. In addition, obesity may be involved in the regulation of chemoreflex function through neurohormonal mediators such as leptin, which decreases when sleep apnea patients lose weight [5]. Thus, these potential mechanisms likely work in concert to act as a vicious cycle in the pathogenesis of OSA and weight body gain (Fig. 2).

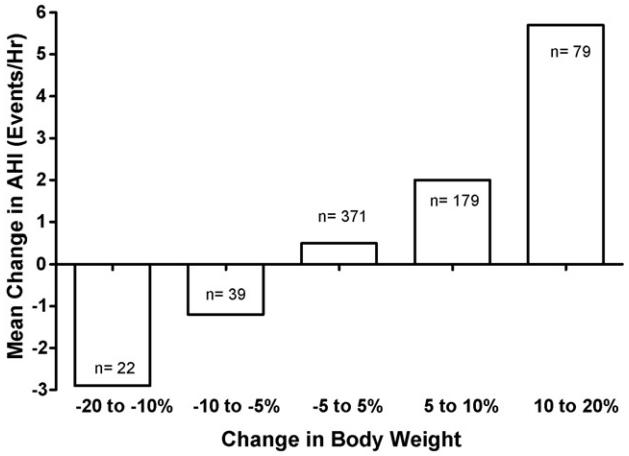

Fig. 1. Effects of weight change on apnea hypoapnea index (AHI) (from [11,22]).

2.1. Gender

It is not entirely clear why sleep apnea is less common in women than men. Nevertheless, several studies indicate that men are at 2–4-fold greater risk for sleep apnea, and recent evidence suggests that this difference may be linked to sex-related distribution of adipose tissue [15,16]. In general, women exhibit less deposition of adipose tissue around the neck and abdomen compared to men, and this has been shown to contribute to risk of sleep apnea [17,5,10]. In obese individuals, adipose tissue deposits surrounding the airway decrease dimensions of the upper airway and contribute to increased airflow resistance [14]. In older men and postmenopausal women, increased fat in the neck and craniofacial areas may increase sleep apnea prevalence [18,19]. Differences in pharyngeal anatomy (i.e., length) and ventilatory stability (dilator muscle activation) may explain some of the gender differences, but it is likely complex and multifactorial [14,20]. In children, however, a link between pharyngeal fat and structure and OSA is not supported by the results of a recent study [21]. Furthermore, epidemiological studies and case reports of OSA and snoring frequency have reported similar preva-

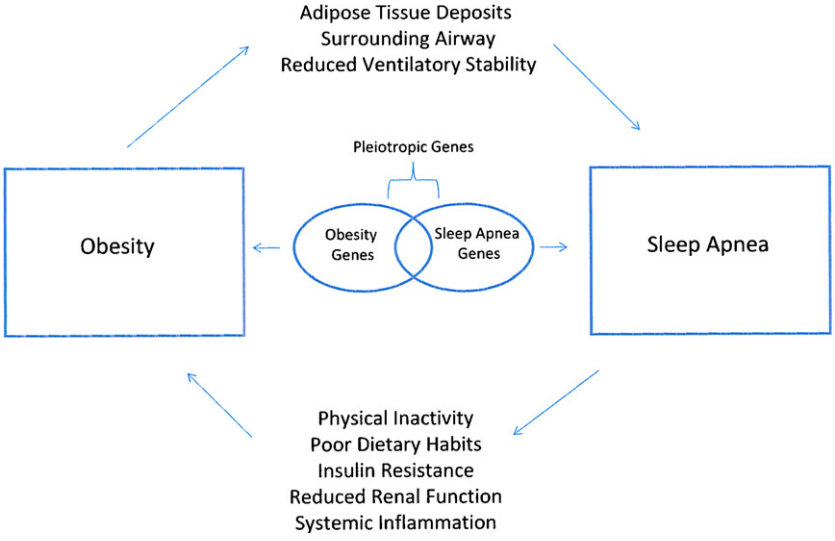

Fig. 2. Proposed mechanisms acting as a vicious cycle in the pathogenesis of obstructive sleep apnea and obesity and the potential influences of shared and non-shared genes.

lence rates among school age boys and girls [22], suggesting other factors likely play a role in adult gender differences.

2.2. Age

Aging has been viewed as a major factor in the pathogenesis of sleep apnea [3,22,15,10]. The highest reported prevalence of OSA is in men 45–64 years old and in women over 65 years of old [22,23]. However, accumulating evidence for increased OSA prevalence in children is changing how clinicians and scientists view age as a risk factor [24].

Recently, one study showed that although the prevalence of OSA may be less in younger individuals, the impact of untreated OSA on behavior, mood, and excessive daytime sleepiness may be more severe. In fact, Castronovo et al. reported that as many as 13% of children between 3 and 6 years old snore frequently and the prevalence of OSA may be as higher as 2–5% in middle school-aged children [25]. In obese children, even higher prevalence rates of OSA and snoring have been reported [26]. Differences in sampling methodology (i.e., questionnaires, respiratory monitoring techniques), definitions of respiratory events, interpretation of polysomnography findings, and populations studied make it more challenging to accurately predict the prevalence of OSA in children and adolescent populations. Given that untreated sleep apnea compromises physical, behavioral, and cognitive development in children, more investigation into mechanisms of these sequelae is needed.

2.3. Race and ethnicity

Most of the inter-ethnic/race studies of OSA in the United States have compared African Americans and Caucasians. Existing data suggest that African Americans exhibit significantly greater risk for OSA and are diagnosed later with more severe OSA [27,3,28,29]. The prevalence of overweight and obesity are also greater in African Americans [1] and along with OSA can contribute to poor health status and quality of life in these individuals. Ancoli-Israel et al. studied community dwelling adults and found that, after adjusting for differences in BMI and other confounding factors, the odds of having an AHI of 30 or greater were 2.5 times greater in African Americans when compared to Caucasians [27]. Data from the Cleveland Family Study showed that shared and unshared genetic factors underlie the susceptibility to OSA and obesity in African Americans, suggesting that genetic determinants of obesity in this population may also determine apnea severity [28].

Limited evidence also suggests that increased OSA prevalence may exist in American Indians and Hispanic adults, due to increased prevalence of childhood and adult obesity [29,9]. High prevalence of OSA has also been reported to significantly impact Asian communities [29,30]. The prevalence rates of OSA have only been recently described in many other Western countries [3,22,25,29] and are not established in many parts of the World.

2.4. Genetics and familial factors

Independently, the genetic determinants for obesity have been described in the literature for several decades [31] and likely play a role in the vicious cycle of obesity and weight gain in some individuals (Fig. 2). Historically, studies from the United States and Europe have reported that the heritability of body weight is estimated to be 50–80% [16,26]. Stunkard et al. found that body weight and size of adopted children was more likely to reflect their biological parents than their adopted ones [32], further supporting the role of heritability in determination of body weight. More recently, several studies have completed genetic scans in obese and non-obese individuals and identified numerous genes associated with heritability of obesity [16].

Whereas, the significant familial linkage to obesity has been known for many years, the genetic determinants and family history of sleep apnea has been described more recently [33,16,26]. Several studies have shown a significant familial and heritability component in the development of clinical obstructive sleep apnea with increasing attention given obese children and their genetic susceptibility to sleep apnea [26]. Patel showed that individuals with relatives with a history of sleep apnea were more than twice as likely to the disease [16].

3. Does OSA promote obesity?

The section above summarizes how obesity causes or exacerbates OSA. Over the last several years, emerging evidence suggests that OSA promotes weight gain and obesity.

OSA repeatedly interrupts sleep and thereby makes adults sleepy during the day. This daytime sleepiness translates into inactivity, and these symptoms correlate with OSA severity. For example, Basta et al. [34] recently reported that log AHI strongly predicted Epworth sleepiness scores, and self-reported physical activity decreased with increasing sleepiness. They also found increased incidence of depression with increased Epworth score in their sample of 365 women and 741 men. An earlier study by Hastings et al. [35] of congestive heart failure patients demonstrated that those with sleep-disordered breathing were objectively much sleepier (Oxford Sleep Resistance Test) and were 7% less active during the day than those without sleep apnea. These investigators also observed negative correlation between AHI and daytime activity.

Effects of sleep disturbance on energy metabolism constitute another possible mechanism for how OSA causes obesity. The first reports of how inadequate or poor-quality sleep, and sleep apnea in particular, adversely affected glucose metabolism appeared in the early 1990s [36–38]. Since then, accumulating data reinforce this finding [39–41]. For example, Tasali et al. [42] recently documented that selective reduction of delta sleep compromises insulin sensitivity.

Hormones known to importantly regulate energy metabolism, such as growth hormone, are secreted during delta sleep. Therefore, the degree to which OSA interferes with delta sleep may in part determine propensity for developing diabetes from OSA. OSA appears to increase secretion of and/or alter responsiveness to the adipocyte hormone leptin and the orexigenic hormone ghrelin, and these effects and their pathophysiologic implications remain subjects of study [43–47].

Medications for co-morbidities of obesity and OSA constitute an iatrogenic source of pathophysiologic exacerbation. For example, type II diabetes and depression are each extremely common in obese patients with OSA, and several classes of drugs commonly prescribed for diabetes and depression promote weight gain as a side effect [48–52]. Therefore, such medications unfortunately help "close the loop" of the vicious cycle between OSA and obesity. Excellent alternatives to medication exist: regular physical activity provides immediate, ongoing, and excellent benefit for treatment of both diabetes [53] and depression [54–57], offers myriad other health benefits, and imposes virtually no negative side effects. In this regard, it would be interesting to know how many doctors sincerely recommend and strongly encourage daily enjoyable physical activity before turning to medications. Depressed patients are often apathetic and lack motivation to exercise, but this simply emphasizes the need for imaginative ways of facilitating enjoyable activity in such patients.

OSA elicits cyclic hypoxemia and hypercapnia with each respiratory event, and these synergistically interact to stimulate acute, and eventually chronic elevation of sympathetic nervous system activity (SNA) [58,59,18]. Chronic and inappropriate sympathoexcitation, in turn, is an established driver of hypertension and cardiovascular disease as well as energy dysmetabolism and diabetes [60–62]. Relative to hypoxemia, the role of hypercapnia in OSA pathophysiology remains much less studied: medline citations of the latter equal about one-third of those for the former. Interactions between the two are interesting and complex; hypercapnia in fact may counteract some deleterious effects of hypoxemia [63,64]. In addition to sympathoexcitation, hypoxemia accentuates free radical formation, which in turn incites the inflammatory response [19]. Growing bodies of work implicate chronic tissue inflammation as a key pathophysiologic mediator of cardiovascular disease, diabetes, dementia, arthritis, and OSA itself [65–69].

Sequelae of obesity and OSA cross all organ systems. For example, chronic excessive musculoskeletal loading from excess weight coupled with sustained tissue inflammation cause arthritis [66]. The associated pain limits activity, which promotes further weight gain. Also, OSA promotes edema formation which of course adds body weight in the form of water [70]. The above discussion summarizes isolated cause–effect relationships that, when linked and integrated into a "big picture", form multiple interwoven vicious cycles between obesity and OSA (http://www.sleepconsultants.com/motherdiagram.html). Nevertheless, some links are more hypothetical than others depending on the number and type of published works that test specific pathophysiologic relationships.

3.1. Does treating OSA with positive airway pressure (PAP) reduce weight?

Given the evidence above that OSA promotes weight gain, it is reasonable to expect that successfully treating OSA facilitates weight reduction. Indeed, Harsch et al. [45] observed that PAP treatment reduced elevated levels of the orexigenic hormone ghrelin by 66% within 2 days of treatment onset, and the same group recently demonstrated a 68% improvement in insulin sensitivity after ∼3 years of successful PAP treatment [71]. Kajaste et al. [72] compared weight loss in two groups of obese male OSA patients: both groups underwent a standardized 2-year weight loss program, but one group used CPAP treatment during the program while the other did not. Surprisingly, CPAP users exhibited similar weight loss to the untreated group.

As we follow patients long-term after they successfully initiate and maintain PAP therapy, our general impression has been that they do not lose weight. As a cursory assessment, we reviewed follow-up data for 28 randomly selected OSA patients (13 women, 15 men) at 8–126 months (mean = 42) after initiation of successful PAP treatment. OSA was severe in 71% of the group. Treatment success was defined as nightly all-night PAP use confirmed by PAP machine data uploads, along with stable arterial oxygen saturation as demonstrated by in-home nocturnal oximetry. Among other queries, our follow-up questionnaire asks patients whether PAP negatively or positively affects their daytime energy levels, physical activity, and exertional dyspnea.

Seventy-nine percent of patients reported increased daytime energy relative to pre-treatment, 64% reported increased activity, and 36% reported reduced exertional dyspnea. Anecdotes include an elderly patient who was delighted that he now mowed his entire yard without stopping to rest (before starting PAP, he had to sit every 10–15 min), a woman who refinished her kitchen cabinets in 1 day (an unthinkable chore prior to PAP treatment), and a father who exhausted his young children with activity at the local park (pre-treatment, he could not be convinced to go to the park). In spite of patient perceptions of increased energy and activity, mean weight *increased* 4% from 106.1 kg (S.D. 23.9) kg at baseline to 110.1 kg (S.D. 23.1) after at least 8 months of chronic successful PAP treatment. Harsch et al. saw no weight reduction with PAP treatment of OSA in two different studies: one with follow-up at 2 months [45], and another with follow-up at 2.9 years [71].

Therefore, current reports and our clinical impressions do not suggest that successful treatment of OSA with PAP leads to weight loss. For the obese patient with severe OSA, associated inactivity, and strong motivation to lose weight, it seems certain that successful PAP treatment would facilitate weight loss, but this remains to be demonstrated.

3.2. The conundrum in children with OSA

Unlike adults with OSA, who usually experience excessive daytime sleepiness, children with OSA commonly develop hyperactivity [7]. In fact, ADHD in children often results at least in part from chronic sleep restriction and/or sleep pathology such as OSA, restless legs syndrome, or periodic limb movement disorder [6,73,74].

Roemmich et al. [7] performed an illuminating study of outcomes following successful treatment of OSA in children. They quantified activity and weight before and 6–27 months after correction of OSA with adenotonsillectomy. Both subjective (parental) assessments of hyperactivity and objective actigraphy showed reduced activity at follow-up: in simplistic terms, fidgeting decreased significantly. Percentage overweight for the group increased from 25% at baseline to 30% at follow-up. Not surprisingly, changes in activity correlated inversely with changes in weight.

These observations imply that treatment of childhood OSA constitutes a prescription for adult OSA. Obviously, OSA in children deserves treatment, but to achieve chronic success, such treatment must be much more comprehensive than simply opening the airway with surgery.

3.3. Physical activity and OSA

Although the etiologies of sleep apnea and obesity are multifactorial and involve complex interaction of many factors, it is clear that poor dietary habits and the lack of physical activity play primary roles in the development of both sleep apnea and obesity. Limited recent results suggest that exercise may reduce the severity of OSA both in association with, and independent of, reduction in body weight. In a retrospective study of questionnaire data from Quan et al. suggested that regular vigorous physical activity of at least 3 h/week may be a useful treatment modality for sleep-disordered breathing [75].

Parental obesity, poor eating behaviors, and lack of physical activity contribute to childhood obesity and play an important role in prevalence of adolescent sleep apnea [3,24,26,76]. Recently, regular vigorous exercise has been shown to improve snoring in overweight children, suggesting that exercise programs may be valuable for prevention and treatment of sleep-disordered breathing in overweight children.

4. Conclusions and future opportunities

The complex pathophysiologic interrelationships between obesity and OSA often defy clear assignment of cause and effect. However, we now know with fair certainty that OSA contributes to weight gain and obesity in a variety of ways. It remains well-established that obesity constitutes the primary risk factor for developing OSA. The Roemmich et al. study [7] and others offer clear lessons: caregivers must adopt more aggressive, early approaches to weight control, to preempt initiation of pathophysiologic vicious cycles. In this regard, the American College of Sports Medicine recently launched the “Exercise is Medicine” initiative (exerciseismedicine.org). In the future, medications may emerge to treat obesity, OSA, and their sequelae with minimal side effects. However, there are effective ways to approach these problems now without waiting for “the magic pill”.

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